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(54) Title: CARVEDILOL METHANESULFONATE

(57) Abstract: This invention relates to carvedilol methanesulfonate, compositions containing this compound and methods of using carvedilol methanesulfonate to treat hypertension, congestive heart failure and angina.

Carvedilol Methanesulfonate

Field of the Invention

This invention relates to a pharmaceutically active compound, compositions containing the compound and methods of using the compound in the treatment of certain disease states in mammals, in particular man. More specifically, the present invention relates to carvedilol methanesulfonate, which is the methanesulfonate salt of 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, compositions containing this compound, and methods of using carvedilol methanesulfonate to treat hypertension, congestive heart failure and angina.

Background of the Invention

U.S. Patent No 4,503,067 describes a compound which is known as carvedilol. This compound is a novel multiple action drug useful in the treatment of hypertension and angina. Carvedilol is known to be both a competitive non-selective β-adrenoceptor antagonist and a vasodilator. The vasodilatory actions of carvedilol result primarily from α_1-adrenoceptor blockade, whereas the β-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug. Also, carvedilol, as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation, is useful in organ protection, in particular, cardioprotection. Additionally, carvedilol is useful in the treatment of congestive heart failure.

The currently marketed formulation of carvedilol is a conventional, swallow tablet and prescribed as a twice-a-day medication in the United States. This formulation is in immediate release form; that is to say the nature of the formulation is such that by the time carvedilol leaves the stomach, it is either in solution or it is in the form of a suspension of fine particles, i.e. a form from which carvedilol can be readily absorbed.

Carvedilol, a free base with one pKa of 7.6, exhibits a predictable solubility behavior in neutral or alkaline media, i.e. above pH 9.0, the solubility is relatively low (< 1 ug/mL). The solubility increases with decreasing pH and eventually reaches a plateau with a broad peak (~ 0.2 mg/mL) at a pH of 4-5. At acidic pHs of 1 to 4 in buffers, the solubility is limited by the solubility of the protonated form of carvedilol or its salt formed in-situ. The hydrochloride salt form formed in-situ in an acidic medium, such as simulated gastric fluid, is less soluble in water than carvedilol itself.

Surprisingly, it has been found that unlike carvedilol or certain salt forms of carvedilol, carvedilol methanesulfonate exhibits a solubility of >8.0 mg/ml in purified water at 25°C. Thus, carvedilol methanesulfonate may result in a dosage form from which

the drug substance becomes available for bioabsorption throughout the gastrointestinal tract. Hence, it may be possible to develop controlled release once-a-day (uid) and twice-a-day (bid) dosage forms, delayed release or pulsatile release dosage forms. Also, carvedilol methanesulfonate may be formulated in an injectible form or as a transdermal patch. The high solubility feature of carvedilol methanesulfonate is particularly important when formulating this compound for therapeutic use.

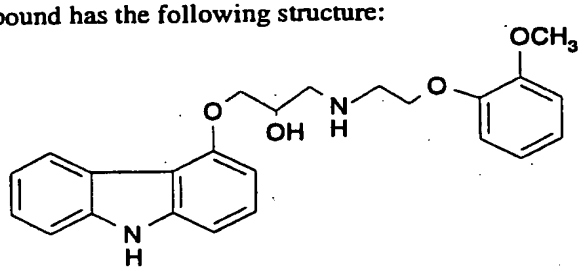
Summary of the Invention

The present invention provides a novel salt form of carvedilol, namely carvedilol methanesulfonate.

The present invention also provides pharmaceutical compositions containing carvedilol methanesulfonate and the use of this compound in the treatment of hypertension, congestive heart failure and angina.

Detailed Description of the Invention

1-(Carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol is known as carvedilol. This compound has the following structure:



and is claimed in U.S. Patent No. 4,503,067 (assigned to Boehringer Mannheim, GmbH, Mannheim-Waldhof, Fed. Rep. of Germany), issued March 5, 1985. Reference should be made to said patent for its full disclosure, including the methods of preparing and using this compound. The entire disclosure of the '067 patent is incorporated herein by reference.

In accordance with the present invention, it has been unexpectedly found that a novel salt form of carvedilol, namely the methanesulfonate salt, exhibits a significantly higher aqueous solubility than the corresponding free base or other prepared salts. The aqueous solubility data for carvedilol and its salt forms determined at 25°C are presented in Table 1.

Table 1 : Aqueous Solubility (mg/mL) at 25°C for Carvedilol and its Salt Forms

Time, hr	Carvedilol (ug/mL)*	Hydrochloride	Adipate	Tartrate	Methanesulfonate
0.5	5.0	1.65	0.46	0.71	8.17
1	9.8	1.63	0.42	0.70	8.40
4		1.37	0.25	0.56	8.67
24	11.6				8.70
70		1.06	0.28	0.68	11.2

*** Note: the solubility of carvedilol is given in micrograms per milliliter.**

The data from Table 1 demonstrates that the methanesulfonate salt of carvedilol exhibits an aqueous solubility in excess of 8 mg/ml, while the hydrochloride, adipate and tartrate salt forms are poorly soluble in water. Thus, the methanesulfonate salt of carvedilol provides for the development of bioenhanced dosage forms and patient-compliant injectible dosage forms.

Carvedilol methanesulfonate salt form can be formulated in accordance with the present invention in an injectible form, an oral solid dosage form (as an immediate release or modified release [i.e. controlled release, delayed release or pulsatile release] capsule or tablet) or as a transdermal patch, in particular, in pharmaceutical compositions for the treatment of congestive heart failure, hypertension and angina.

By controlled release is meant any formulation that achieves slow release of drug over an extended period of time. In the controlled release formulations of the instant invention, a portion of the carvedilol methanesulfonate in the formulation is made available as a priming dose and the remainder is released in a sustained fashion. Examples of controlled release systems are a matrix tablet or bead formulation, and a barrier film coated tablet or bead/pellet formulation.

By delayed release is meant any formulation wherein the release of the drug is delayed for certain time or minimum under acidic conditions but rapid above a certain pH depending on the polymer used for the barrier film coat. Examples of delayed release systems include timed-release tablets and capsules and enteric-coated tablets and beads.

By pulsatile release is meant any multi-unit tablet or capsule formulation where in individual mini-tablets or particulates/pellets/beads are polymer barrier film coated, that utilizes intermittent pulsatile dosings of carvedilol methanesulfonate from one or more units as a function of time.

Such modified release formulations are preferably formulated in a manner such that release of carvedilol methanesulfonate is affected predominantly during the passage through the stomach and the small intestine to the colon.

Examples of controlled release, pulsatile release and delayed release formulations which are suitable for incorporating carvedilol methanesulfonate are described in:

Sustained Release Medications, Chemical Technology, Review No. 177, Ed. J.C. Johnson, Noyes Data Corporation (1980);

Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition, Eds. J.R. Robinson, V.H.L. Lee, Mercel Dekkes Inc., New York (1987);

Remington's Pharmaceutical Sciences, 16th Edition, Ed. A. Osol, Mack Publishing Company (1980); and

Solubility Considerations and Design of Controlled Release Dosage Forms, by G.M. Venkatesh, Polymer Preprint, Volume 40, pp 322, 1999 (American Chemical Society).

The process for preparing the solid dosage forms in accordance with the present invention may be carried out using a combination of a planetary mixture, a V-blender, a high shear granulator, a fluid bed granulator, a slugging press, a roller compactor, a cummunuting mill, sieving equipment, or a tableting machine. Optionally, the granulation of the hydrated or anhydrous form of carvedilol methanesulfonate, produced using a conventional dry or wet granulating equipment, is suitable for the preparation of immediate or modified release dosage forms. The preferred unit dosage forms include tablets or capsules. The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable pharmaceutically acceptable carriers for use in this invention include diluents, fillers, binders and disintegrants. An intra-venous formulation is prepared by methods known in the industry.

Immediate and modified release matrix beads may be manufactured using a extrusion-spheronization system. A wet granulated mass suitable for extrusion is prepared by blending the drug, a binder and a diluent or a matrix forming polymer, processing through a extrusion-spheronization system and collecting beads of a desired size fraction. The release profiles of the drug from these beads may further be modified by applying a barrier film coat. A buffer-based membrane-coated bead formulation may also be manufactured by a slurry-coating process as discussed in Pharmaceutical Development and Technology, Volume 3, pp 477-485 (1998). Alternately, transdermal patches for administration of carvedilol methanesulfonate through the skin at a predetermined rate can also be manufactured.

Any combination of pharmaceutically acceptable excipients, e.g. buffers, carbohydrates, diluents, fillers, binders and disintegrants, in desired proportions may be

utilized in accordance with the wet or dry granulation process or direct compression formulation of the present invention. The excipients commonly used in pharmaceutical industry are well described in the literature [refer to the Handbook of Pharmaceutical Excipients, A. Wade and P. J. Weller (Editors), American Pharmaceutical Association (1994)]. Pharmaceutically acceptable fillers and diluents include, but are not limited to, the following: lactose (hydrous as well as anhydrous), starch [unmodified (corn starch) or modified (for example, Starch 1500 available from Colorcon)], sucrose, mannitol, sorbitol, cellulose, inorganic sulfates and phosphates. Disintegrants include, but are not limited to, the following: sodium starch glycolate, sodium carmellose and crosslinked polyvinyl pyrrolidone, and binders include, but are not limited to, the following: gelatin, corn starch, modified starch (Starch 1551, pregelatinized starch), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxy methyl cellulose, alginic acid, acacia, etc. Examples of excipients suitable for modified release applications include, but are not limited to, the following: high molecular weight HPMCs, polymethacrylate polymers known as Eudragits, polyethylene oxide, Polyox® (Union Carbide Corporation), modified ethyl cellulose, Surelease® (Colorcon), crosslinked acrylic acid polymers, Carbopol® (BF Goodrich Speciality Chemicals) and waxy materials, such as glyceryl behenate (Compritol®, glyceryl palmitostearate (Precirol®), and Gelucires® [all from Gattefosse s.a., France] and carnauba wax.

The matrix formulations of the present invention may be prepared using three types of materials: insoluble plastics, hydrophilic polymers or fatty compounds. Plastic matrices include methyl acrylate-methacrylate, polyvinyl chloride and polyethylene. Hydrophilic polymers include methylcellulose, hydroxypropylmethylcellulose (HMPC) and sodium carboxymethylcellulose. Fatty compounds include various waxes such as carnauba wax and glyceryl tristearate. The most common method of preparation is to mix carvedilol with the matrix material and then compress the mixture into tablets. In the case of wax matrices, carvedilol is generally dispersed in molten wax, which is then congealed, granulated and compressed into cores. In the matrix formulation containing carvedilol, the priming dose (the portion of the carvedilol that is immediately available in the formulation) is placed in a coat of the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating.

Delayed release formulations containing carvedilol methanesulfonate may be prepared either by coating particles or granules or tablets with enteric polymers which are resistant to acids but soluble at alkaline pHs. Examples of enteric polymers are hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate or butyrate, polyvinyl acetate phthalate, Eudragit L and S polymers. Thus, the release of carvedilol methanesulfonate can be controlled by adjusting the thickness of the barrier coat and/or by

a proper choice of the enteric polymer. The coated particles can be filled into capsules or optionally compressed into tablets.

The present invention also provides for various combinations of immediate release and controlled release forms. For example, the uncoated sustained release matrix core may be in combination with an immediate release form of carvedilol methanesulfonate and/or a coated matrix form. The matrix core may be comprised of a multitude of pellets coated independently with different release-delaying substances, all of which may be combined with uncoated or immediate release forms of carvedilol methanesulfonate.

The present invention provides a method of treating hypertension, angina and congestive heart failure by administering an effective amount of an immediate release or controlled release or delayed release formulation containing carvedilol methanesulfonate, or a combination thereof, for treating hypertension, angina and congestive heart failure. The formulations of the instant invention may also be used in organ protection, for example, in cardioprotection.

The following examples are illustrative of the instant invention. These examples are not intended to limit the scope of this invention as defined hereinabove and as claimed hereinbelow.

In Examples 2-5, below, the term "internal granules" means the granulation obtained by blending and granulating ingredients (drug substance and excipients) by a wet or dry granulation process.

Examples

Example 1

Preparation of carvedilol methanesulfonate: Carvedilol was suspended in an aqueous solution of methanesulfonic acid, with the acid being present at a 1:1 molar ratio. The suspension is vortexed during the addition of carvedilol powder. After storage of the suspension for 6-15 hrs, the suspension is filtered and the solid residue is dried.

Example 2

56.0 parts of carvedilol methanesulfonate, 40 parts of powdered mannitol and 4.0 parts of pregelatinized starch (Starch 1551), a binder are granulated in a planetary mixer using purified water as the granulating agent. The moist granulation is wet milled and dried using a fluid bed drier or an appropriate drying device. The dried granulation is milled to produce granules passing through a #30 mesh or appropriate size sieve. Compression mixes with ingredients as listed in Formulas 1 and 2 are prepared by blending and compressed into 30.0mg (as carvedilol free

base) tablets with a tensile strength in the range of 3-10 kP using a tablet press. Tablets of Formulas 1 and 2 disintegrate in less than 2 minutes when tested in purified water at 37°C.

Ingredients (mg/tab)	Formula 1	Formula 2
Internal granules	68.7	68.7
Microcrystalline cellulose	-	7.5
Crospovidone, crosslinked PVP	3.6	3.0
Magnesium stearate	0.7	0.8
Total	73.0	80.0

Example 3

56.0 parts of carvedilol methanesulfonate, 40 parts of fumaric acid and 4.0 parts of PVP, a binder, are dry granulated using a chilsonator, a Fitzmill and sieve-shaker to produce granules passing through a #30 mesh or appropriate size sieve. Compression mixes with ingredients as listed in Formulas 3 and 4 are prepared by blending and compressed into 30.0 mg tablets of hardness in the range of 5 - 10 kP using a tablet press.

Ingredients (mg/tab)	Formula 3	Formula 4 (DC Formula)
Carvedilol methanesulfonate		38.5
Internal granules	68.7	
Microcrystalline cellulose	20.5	15.5
Spray dried lactose		26.0
Crospovidone, crosslinked PVP		4.0
Magnesium stearate	0.8	1.0
Total	90.0	85.0

Example 4

56.0 parts of carvedilol methanesulfonate, 32.0 parts hydroxypropylmethyl cellulose (Methocel E4M, from Dow Chemical Co.), 8.0 parts of Methocel E15LV, 4.0 parts crosslinked polyvinylpyrrolidone (Crospovidone) and 4.0 parts of pregelatinized starch (Starch 1551), a binder are granulated in a planetary mixer using purified water as the granulating agent. The moist granulation is wet milled and dried using a fluid bed drier or an appropriate drying device. The dried granulation is milled to produce granules passing through a #30 mesh or appropriate size sieve. A compression mix is prepared by blending 68.7 parts of

the granulation and 0.8 part of magnesium stearate and compressed into 30.0 mg tablets releasing the drug at a predesigned fashion.

Modified Release Formulations

Example 5

80.0 parts of carvedilol methanesulfonate, 5.0 parts of hydroxypropylmethyl cellulose, and 15% glyceryl behenate (Compritol) are blended, roller compacted, milled using a Fitzmill milled to produce granules passing through an appropriate size sieve. Compression mixes with ingredients as listed in Formulas 5 and 6 are prepared by blending and compressed into 30.0 mg tablets. Tablets of Formula 6 disperse rapidly in the dissolution medium or on oral administration, and the drug is released from the granules over a long period.

Ingredients (%)	Formula 5	Formula 6
Internal granules	48.1	48.1
Microcrystalline cellulose	11.2	33.1
Crospovidone, crosslinked PVP		3.0
Magnesium stearate	0.7	0.8
Total	60.0	85.0

Example 6

Tablets of Formulas 1 and 2 are applied a membrane barrier coat using Eudragit RL polymer to provide for a long lasting release profile. Tablets of Formulas 3 and 4 are provided with an enteric coat using Eudragit L30D to produce delayed release dosage forms. A seal-coat and an over-coat are optionally applied to the tablets of these formulations.

Example 7

80 parts of carvedilol methanesulfonate, 10 parts microcrystalline cellulose and 10 parts of Povidone (PVP) are granulated, extruded and spheronized using microcrystalline cellulose for dusting. Dried beads of a desired size fraction are also coated with a Surelease formulation to provide a barrier membrane of different thicknesses. Uncoated and coated beads at desired proportions are filled into hard gelatin capsules

Example 8

Non-pareil sugar seeds are layered with carvedilol methanesulfonate by slurry coating in a fluid bed granulator a suspension of the drug and talc in an aqueous Povidone solution. The pellets are hot melt coated with a waxy formula listed below, and cured for 12 hrs at 40°C..

Pellet	%W/W(approx)
Non Pareil Seed	39
Carvedilol	49
Povidone	10
Talc	2

Coating	%w/w
Glycerylmonostearate	37
Glyceryldistearate	53
White Wax	10

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

The various references to journals, patents, and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound which is carvedilol methanesulfonate.

2. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

3. A controlled release formulation comprising the compound according to claim 1 in dosage unit form.

4. A delayed release formulation comprising the compound according to claim 1 in dosage unit form.

5. A matrix formulation comprising the compound according to claim 1 in dosage unit form.

6. An enteric coated formulation comprising the compound according to claim 1 in dosage unit form.

7. A method of treating hypertension, congestive heart failure or angina which comprises administering to a subject in need thereof an effective amount of the compound according to claim 1.

8. A compound according to claim 1 for use as a medicament.

9. The use of a compound according to claim 1 in the manufacture of a medicamnet for the treatment of hypertension, congestive heart failure or angina.

10. A process for the preparation of carvedilol methanesulfonate which comprises reacting carvedilol with an aqueous solution of methanesulfonic acid, with the acid being present at a 1:1 molar ratio.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/411; 548/444; 424/448, 449, 457, 468, 474, 490

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 4,503,067 A (WIEDEMANN et al) 05 March 1985 (05.03.1985)	1, 2, 7-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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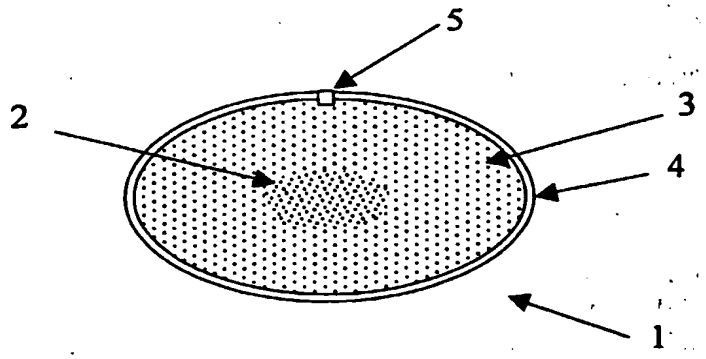
(54) Title: COMBINED DIFFUSION/OSMOTIC PUMPING DRUG DELIVERY SYSTEM



(57) Abstract: A delivery device [(1) in Figure 1a] capable of delivering one or more active substances by diffusion through plural micropores in the membrane (4) or by osmotic pumping through one or more performed passageways (5) in the membrane is provided. The device (1) contains a centrally located expandable core (2) completely surrounded by an active substance containing layer (3), which is completely surrounded by the membrane (4). The device is capable of delivering insoluble, slightly soluble, sparingly soluble and very soluble active substances to an environment of use. The preferred delivery rate is zero order. The device can deliver an active substance for a period of about 12-24 hours.

WO 01/51035 A1

COMBINED DIFFUSION / OSMOTIC PUMPING DRUG DELIVERY SYSTEM

INVENTOR

JOAQUINA FAOUR

FIELD OF THE INVENTION

This invention pertains to a delivery device for the controlled release of active agents to an environment of use. More particularly, the invention pertains to a device for the delivery of active agents over a prolonged and extended period of time. The controlled delivery device comprises an expandable-hydrophilic polymer-core located substantially in the center of the dosage form surrounded by a composition of the active agent(s) to be delivered. A novel dual function membrane permits delivery of the active agent(s) through a combination of diffusion and osmotic pumping mechanisms.

BACKGROUND OF THE INVENTION

Osmotic devices have demonstrated utility in delivering beneficial active agents, such as medicines, nutrients, food, pesticides, herbicides, germicides, algaecides, chemical reagents, and others, to an environment of use in a controlled manner over prolonged periods of time. Known devices include tablets, pills, and capsules.

Several advancements have been made in the art to improve the delivery of insoluble or slightly soluble products to an environment of use. The prior art has focused on the development of new membranes that deliver active agents by diffusion and/or osmotic pumping.

U.S. Patent No. 4,235,236 to Theeuwes discloses an osmotic device that delivers drug by the combined mechanisms of diffusion and osmotic pumping. The device comprises a microporous wall surrounding a compartment containing an active agent and an expandable member. The expandable member consists of a semipermeable, flexible or expandable film surrounding a member selected from the group consisting of an osmotically effective solute, a gas generating couple and a swellable polymer. The external wall of the device is formed of a microporous material through which the active agent is

delivered. This patent does not disclose the inclusion of a passageway in the external wall to provide delivery by osmotic pumping and diffusion. Even though the solution proposed by US Patent 4,235,236 allows the release of an active agent at a steady rate – the so called zero-order release-, it requires the manufacturing of an elastic film that separates the expandable member from the composition comprising the active agent. The adhesion process between said membrane and said composition comprising the active agent requires complicated processing steps that make the formulation very expensive.

U.S. Patent No. 4,327,725 to Cortese and Theeuwes, discloses an osmotic device comprising a semipermeable wall surrounding two layers, one layer containing an active agent and the other an expandable hydrogel. A passageway in the wall communicates the active agent layer with the environment of use. The patent describes the use of cellulose acylate as the material comprising the semipermeable membrane.

U.S. Patents No. 5,612,059 and No. 5,698,220 to Cardinal et al., disclose the use of asymmetric membranes in delivery devices. These membranes may be permeable, semipermeable, perforated or unperforated and can deliver an active substance by the combined mechanisms of diffusion and osmotic pumping. These patents also disclose the formation of asymmetric membranes with 398-10 (Eastman) cellulose acetate.

EP 636366 and EP 553392 disclose an active agent composition coated with an aqueous dispersion of plasticized acrylic polymer, which is subjected to a particular curing process. The controlled release formulation disclosed in these applications has a stable dissolution profile despite exposure to a variety of storage conditions.

U.S. Patent No. 5,543,155 to Fekete et al. discloses a controlled delivery pharmaceutical composition core surrounded by a wall comprising an ammonium methacrylate copolymer that is permeable to low molecular weight (MW) molecules. This controlled delivery pharmaceutical composition contains an active pharmaceutical compound and hydroxypropyl methylcellulose (HPMC) as the hydrophilic polymer. Low MW osmagents are not incorporated into the composition. Tablets having a bi-layered core are prepared with a hydrophilic polymer layer comprising high molecular weight HPMC, which has a viscosity higher than 1000cP in a 2% aqueous solution.

U.S. Patent No. 5,543,155 also discloses various combinations of Eudragit™ RL (easily permeable films) and Eudragit™ RS (not easily permeable films). The use of a permeable membrane alone, however, does not allow the inclusion of a low molecular weight osmotic agent in the pharmaceutical composition tablet core (for example, potassium chloride, sodium tartrate, sodium chloride, sodium sulfate, etc.). Thus, it limits the versatility of the device to the delivery of active agents that require a significant absorption of liquid to achieve an effective and constant delivery of solution or suspension of the active agent from the device. Osmotic devices having a bi-layered core, one layer containing the active agent and the other being a swellable placebo layer, surrounded by a semipermeable membrane possess significant disadvantages. The placebo layer consists mainly of a swellable polymer and/or a hydrogel that, while absorbing fluid from the environment of use, expands and exerts pressure over the layer that contains the active agent thereby releasing the active agent through a passageway in the wall. The prior art teaches that perforation of the semipermeable membrane needs to be carried out selectively on the side of the membrane that is adjacent to the layer comprising the active agent. In fact, if the membrane is perforated adjacent the placebo layer, the active agent will not be released. If two perforations are carried out, one adjacent the active-agent layer and the other adjacent the swellable polymer layer ("push" layer), both the active agent and the swellable polymer are released, resulting in loss of the "push" effect. The device would therefore act as a simple osmotic pump that would not allow the release of the entire charge of active agent in the dosage form. The precise selection of which portion of the membrane should be drilled requires the use of color or shape coding in order to distinguish the layers, as well as meticulous handling of the devices. The handling of the devices requires the use of sophisticated and expensive electronic equipment able to recognize the different layers of the tablet core.

U.S. Patent No. 5,543,155 also discloses perforation of the membrane adjacent both layers of the core; however, a specific high molecular weight polymer (HPMC) is required to prevent the loss of the push layer leaving a significant number of available hydrophilic polymers unavailable for use in these devices.

U.S. Patent No. 5,516,527 to Curatolo discloses a device that can include a preformed passageway and plural pores. The device requires the formation of a phase-separated coating that ultimately forms a porous membrane.

While the prior art discloses a wide variety of osmotic devices, no single device has been found to be generally applicable and, in fact, most known devices are designed to operate within a relatively narrow range of conditions. For example, a first formulation of an osmotic device may be generally useful for delivering slightly to sparingly water soluble components to an environment of use, but that same formulation will require drastic changes in order to deliver a very water soluble component and vice versa. In addition, diffusion controlled devices are generally useful for delivering sparingly to very, but not slightly, water soluble components to an environment of use. Therefore, a need remains for a delivery device capable of delivering components having very different solubilities to an environment of use without requiring a dramatic reformulation of the device.

SUMMARY OF THE INVENTION

The present invention provides a controlled release device for active substances comprising an external dual delivery membrane having at least one preformed passageway and plural micropores, wherein the device releases the active agent through a combination of diffusion and osmotic pumping. The at least one passageway can be located anywhere in the dual delivery membrane.

The present invention also provides a controlled release device having an approximately centrally located core comprising a hydrophilic expandable polymer and, optionally, an osmagent, wherein the core is surrounded by a composition comprising at least one active agent and preferably an osmagent and/or an osmopolymer. During operation in an environment of use, the hydrophilic core imbibes fluid and increases in volume thereby forcing release of the active agent(s) through either the pores of the membrane by diffusion and/or the passageway by osmotic pumping effect.

The invention also provides a therapeutic device for the delivery of pharmaceutically active agents, ranging in solubility from slightly soluble to very soluble

drugs, in a controlled, continuous and approximately steady, preferably zero order, rate over a prolonged period of time.

The invention also provides a smaller than usual dosage form that delivers active compounds by diffusion through the entire surface of the device. In this way, a portion of the membrane that releases active compounds is doubled with respect to conventional bi-layered devices.

The invention also provides a controlled release device containing a high or low molecular weight osmagent inside the core of the device, thereby enabling the device to absorb greater quantities of fluid, deliver a greater range of active agents irrespective of their solubilities, and deliver the active agents by diffusion and/or osmotic pumping.

The device of the present invention may optionally be provided with an external coating comprising one or more active agents for immediate delivery to the environment of use.

Accordingly, one aspect of the present invention provides an improved device for the controlled delivery of active agents to an environment of use, wherein the device comprises:

a) a core located approximately at the center of the device and comprising at least one expandable hydrophilic polymer and optionally an osmagent, the core being able to absorb and/or imbibe fluids from one environment of use;

b) a composition immediately surrounding the core comprising at least one active substance and, optionally, an osmagent and/or an osmopolymer;

c) a membrane immediately surrounding the composition and comprising a mixture of a cellulose acylate (ester), a methacrylate salt copolymer and a plasticizer, wherein the membrane permits delivery of the at least one active substance through a combination of diffusion and osmotic pumping; and

d) at least one preformed passageway and plural micropores in the membrane that communicate the composition with the outside of the device.

Active agents can include compounds such as biologically or pharmacologically active agents, medicines, nutrients, food products, insecticides, pesticides, herbicides, germicides, algaecides, fungicides, chemical reagents, growth regulating substances,

parasiticides, sex sterilants, fertility promoters, biocides, rodenticides, disinfectants, anti-oxidants, plant growth promoters, preservatives, fermentation agents, fertility inhibitors, deodorants, micro-organism attenuators, catalysts, food supplements, cosmetics, vitamins, and other agents that benefit the environment of use.

Preferred embodiments of the invention include those wherein the active substance is pharmacologically or biologically active or wherein the environment of use is the GI tract of a mammal.

Other preferred embodiments of the device of the invention are used in biological environments including the oral, ocular, nasal, vaginal, glandular, gastrointestinal tract, rectal, cervical, intrauterine, arterial, venous, otic, sublingual, dermal, epidermal, subdermal, implant, buccal, bioadhesive, mucosal and other similar environments. Likewise, it may be used in aquariums, industrial warehouses, laboratory facilities, hospitals, chemical reactions and other facilities.

Other features, advantages and embodiments of the invention will become apparent to those of ordinary skill in the art by the following description, accompanying examples and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are given by way of illustration only, and thus are not intended to limit the scope of the present invention. The drawings are not drawn to scale.

Figure 1-a is a sectional view of an oral device according to the present invention. Figure 1-b is a sectional view of the device of Figure 1-a, wherein the core has been expanded by imbibing a fluid.

Figures 2 to 4 depict active agent release diagrams using the devices of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1-a depicts an oral dosage form device (1) comprising an approximately centrally located core (2) comprising an expandable hydrophilic polymer composition capable of absorbing, or imbibing, fluids. The core (2) is surrounded by and in contact

with a layer (3), which comprises at least one active agent and optionally an osmotically effective solute. The layer (3) is surrounded by and in contact with a wall (4) having pores (not shown) and a preformed passageway (5). The device delivers the active agent by diffusion and osmotic pumping. The wall (4) is preferably physiologically inert and preserves its physical and chemical integrity during delivery of the active agents comprised in the layer (3).

The beneficial agent(s) comprised in the layer (3) is delivered from the delivery device (1) generally as follows. Fluid is imbibed from an environment through the membrane (4) into the device (1). The fluid then permeates the layer (3). The hydrophilic core (2) imbibes the fluid and swells pushing the aqueous solution or suspension formed from the layer (3) towards the membrane (4). The beneficial agent is released from the dosage form by molecular diffusion across the membrane (4) and/or by osmotic pumping through the passageway (5) in the membrane.

Figure 1-b depicts the device of Figure 1-a in operation delivering the active agent in the layer (3). During operation, the hydrophilic polymer composition of the core (2) absorbs fluid that enters the device (1) across the wall (4) and swells, or expands. Figure 1-b depicts the enlarged core pushing the active agent through the wall and passageway.

The layer preferably completely surrounds the expandable core, thereby promoting isotropic diffusion and thus providing an about zero order release profile.

The inclusion of an about centrally located expandable hydrophilic polymer core in the present delivery device allows delivery of the active agent by isotropic diffusion, thus providing a steady release rate, that is about zero order release profile. The isotropic diffusion process provides a release profile closer to the desired zero order release profile while anisotropic diffusion provides a release profile with an accelerated initial release.

The portion of active agent that is delivered by diffusion or osmotic pumping generally depends upon the diffusivity of the active agent through the wall (4) and/or the solubility of the active agent. When the beneficial agent is poorly soluble in water and has a low diffusivity, the aqueous suspension of the active agent composition of layer (3) is mainly released to the environment of use across the at least one passageway (5) of the wall in a controlled manner over a prolonged period of time. In the case of water soluble

active agents, the increase in concentration of the active agent in the solution adjacent the membrane (4) will effect release of the active agent by diffusion. Additionally, the swelling of the expandable hydrophilic polymer core contributes to the complete release of the solution at a substantially steady rate, minimizing diffusional resistance of the boundary layer.

As used herein, the terms "very soluble", "freely soluble", "soluble", "sparingly soluble", "slightly soluble", "very slightly soluble", and "practically insoluble" or "insoluble" are defined as they are defined in the U.S.P. 23rd Ed. as follows:

Term	Solubility of component in water (parts of solvent per part of component)
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1,000
Very slightly soluble	1,000-10,000
Practically insoluble of insoluble	Over 10,000

The formulation of the present delivery device can be changed according to the following guidelines to permit delivery of slightly, sparingly and very soluble active agents. The following guidelines are applicable to embodiments of the delivery device intended for use in an aqueous environment.

For slightly water soluble active agents, such as allopurinol, amoxicilin, aspirin, cefazolin, cimetidine, hydrochlorothiazide, nifedipine, and cisapride monohydrate, the active agent is preferably delivered through the preformed passageway. The core preferably comprises an expandable hydrophilic polymer, such as HPMC, methylcellulose (MC), carboxymethylcellulose sodium (CMC-Na), and poly(alkylene oxides), and/or an osmagent, such as NaCl, mannitol, dextrose, sodium tartrate, and sodium acetate. The

layer surrounding and in contact with the core preferably comprises the active substance, an osmopolymer, and an osmagent. The wall surrounding and in contact with the layer containing active agent preferably comprises a cellulose ester, such as cellulose acetate, cellulose propionate, and cellulose acetate-butyrate, a polymethacrylate copolymer, such as poly(ammonium methacrylate) copolymer and (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)ethyl methacrylate], and a plasticizer, such as PEG 400, PEG 6000, triacetin and glycerin. The cellulose ester, polymethacrylate copolymer and plasticizer are preferably present in the ratio of 0.1 – 99.8 wt. cellulose ester: 0.1 – 99.8% wt. polymethacrylate copolymer: 0.1 – 25% plasticizer. For very water soluble active agents, such as meperidine HCl, buspirone HCl, diltiazem HCl, oxybutynin HCl, ranitidine HCl, pseudoephedrine HCl, and venlafaxine HCl, the active agent is delivered through both the preformed passageway and the micropores of the wall. The core preferably comprises a hydrophilic expandable polymer and an osmagent. The layer surrounding and in contact with the core preferably comprises the active substance, and a hydrophilic expandable polymer and an osmagent. The wall surrounding and in contact with the layer containing active substance preferably comprise a cellulose ester, a poly(methacrylate) copolymer, and a plasticizer.

For sparingly water soluble active substances, such as caffeine, ciprofloxacin HCl, enalapril maleate, and metronidazole, the active agent is delivered through both the preformed passageway and the micropores of the wall. The core preferably comprises an expandable hydrophilic polymer, and an osmagent, such as. The layer surrounding and in contact with the core preferably comprises the active substance, an osmopolymer and an osmagent. The wall surrounding and in contact with the layer containing active agent preferably comprises a cellulose ester, a polymethacrylate copolymer, and a plasticizer. The cellulose ester, polymethacrylate copolymer and plasticizer are preferably present in the ratio of 0.1-99.8% wt. cellulose ester : 0.1-99.8% wt. polymethacrylate copolymer : 0.1-25% plasticizer.

The micropores in the wall are not formed by mechanical means. The micropores are formed during preparation of the wall or during exposure to fluids in an intended environment of use. Methods of preparing walls wherein the micropores form in the

environment of use are well known and described in, among others, U.S. Patents No. 3,845,770, No. 3,916,899, No. 4,063,064, No. 4,088,864, No. 4,816,263, No. 4,200,098, No. 4,285,987 and No. 5,912,268, the relevant disclosures of which are hereby incorporated by reference.

Swellable hydrophilic polymers suitable for manufacturing the core (2) include hydrophilic polymers that interact with water and/or aqueous biological fluids, and swell and retain water within their structure. The core preferably expands to about 2 to 50 times its initial volume. The polymers are preferably slightly cross-linked. Uncross-linked polymers will preferably not dissolve in water, keeping their physical integrity. The polymers are of animal, plant or synthetic origin. Hydrophilic polymers suitable for manufacturing the core of the invention preferably include hydroxypropyl methylcelluloses (viscosity from 3 to 100,000 cps, measured in 2% w/v solution); ethylcelluloses (viscosity from 3 to 110 cP, measured in 5% w/v solution); methylcelluloses (viscosity from 10 to 10,000 cP, measured in 2% w/v solution); hydroxypropylcelluloses (general average molecular weight of about 80,000 to 1,150,000); hydroxyethylcelluloses (viscosity from 2 to 21,000 cP, measured in 2% w/v solution); carboxymethylcelluloses (viscosity from 5 to 4,000 cP, measured in 1% w/v solution); poly (alkylene) oxide that might include homopolymer of ethylene oxide, propylene oxide and butylene oxide and copolymers of those.

The poly(alkylene oxides) used herein preferably have an average molecular weight of about 1,000,000 to 2,000,000 (viscosity around 400-800 and 2,000-4,000 cP, measured in 2% w/v solution), or an average molecular weight around 4,000,000 to 8,000,000 (viscosity around 1,650-5,500 and 10,000-15,000 cP, measured in 1% w/v solution).

The membrane, or wall, (4) according to the invention preferably comprises a mixture of cellulose esters (CE), copolymers of methacrylate salts (CM) and a plasticizer (P). The active agent is released in a controlled manner through the membrane (4) by the combined mechanisms of diffusion and osmotic pumping. The ratio CE:CM:P is preferably about 1-99% of CE : about 84-0.5% of CM weight : about 15-0.5% of P by weight. The ratio of these ingredients is varied to control delivery of active agents either

predominantly by diffusion across the surface of the membrane (4) to predominantly by osmotic pumping through the passageway (5) and combinations thereof.

Representative cellulose esters useful in the membrane of the invention include cellulose acylate; mono, di and tricellulose alkanylates; mono, di and tricellulose aroylates; cellulose propionate; cellulose acetate-butyrate; cellulose triacylates such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate; cellulose diacylates such as cellulose disuccinate, cellulose dipalmitate; combinations thereof and other cellulose esters used by those of ordinary skill in the art in the preparation of controlled delivery devices and membranes.

The poly(methacrylate) copolymer salts used in the manufacturing of the membrane (4) are preferably insoluble in water and in digestive fluids, but films made therefrom are preferably permeable to dissolved substances to different degrees. Preferred copolymers include: poly(ammonium methacrylate) copolymer RL (Eudragit™ RL), poly(ammonium methacrylate) copolymer (type A-USP/NF), poly(aminoalkyl methacrylate) copolymer RL-JSP I), and (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)-ethylmethacrylate] (1:2:0.2) copolymer, MW 150,000. More preferred polymers include (Röhm Pharma, Weiterstadt): Eudragit™ RS 100: solid polymer, Eudragit™ RL 12.5: 12.5% solution in solvent, Eudragit™ RL 30 D: 30% aqueous dispersion, and other equivalent products.

The following poly (ammonium methacrylate) copolymers can also be used: ammonium methacrylate copolymer RS (Eudragit™ RS), poly(ammonium methacrylate) copolymer (type B-USP/NF), poly(aminoalkyl methacrylate) copolymer (RSL-JSP I), (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)-ethyl methacrylate] (1:2:0.1) copolymer, PM 150,000. More preferred polymers include (Röhm Pharma, Weiterstadt): Eudragit™ RS 100: solid polymer, Eudragit™ RS 12.5: 12.5% solution in solvent, Eudragit™ RS 30 D: 30% aqueous dispersion and other equivalent products. Eudragit™ RL is readily water permeable while Eudragit™ RS is hardly water permeable. By employing mixtures of both Eudragit™ RL and Eudragit™ RS, membranes having the desired degree of permeability are prepared.

The porosity of the wall will vary according to its composition. A highly porous wall is preferably used to deliver slightly soluble active substances. A highly porous wall will provide a faster release of drug than a slightly porous wall. A slightly porous wall is preferably used to deliver very soluble active substances. A moderately porous wall is preferably used to deliver moderately soluble active substances. A moderately porous wall will provide a faster release of drug than a slightly porous wall.

Plasticizers that can be used in the membrane of the invention include all those that are generally incorporated into polymeric coatings of delivery devices. Plasticizers generally improve the mechanical properties and increase the flexibility of the polymeric film. Plasticizers generally reduce cohesive intermolecular forces and increase mobility of polymer chains, thus reducing polymer-polymer interactions. This action is responsible for the changes to the properties of the polymers and films thereof such as a reduction of Tg (glass transition temperature) or softening temperature and the elastic module, increasing polymer flexibility, thus facilitating the process of formation of the membrane or film. A preferred pharmaceutical plasticizer is non-toxic and non-irritating; has a reduced tendency to migrate, extrude or volatilize; and has good miscibility with the polymers in film. Plasticizers that are used in the wall of the present invention include, for example, acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, polyethylene glycol, triacetin, propylene glycol, dibutyl phthalate, diethyl phthalate, isopropyl phthalate, dimethyl phthalate, dactyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, fractionated coconut oil, and others. Preferably, polyethylene glycol is used, for example PEG 400, which is available from suppliers such as Aldrich, Sigma Chemical Co. and others.

Suitable plasticizers also include, by way of example and without limitation, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol esters, poly(propylene glycol), multi-block polymers, single-block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin. Such plasticizers can also include ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol

and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutylsebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co. A combination of plasticizers may also be used in the present formulation. The PEG based plasticizers are commercially available or can be made by a variety of methods, such as disclosed in *Poly (ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J.M. Harris, Ed.; Plenum Press, NY) the disclosure of which is hereby incorporated by reference.

The passageway (5) in the membrane (4) that connects the inside of the delivery device (1) with the outside allows release of the active agent to the environment of use. Exemplary passageways include an orifice, hole, bore, aperture or the like, through which the active agent is released. Mechanical perforation, laser perforation or any other method known to the artisan of ordinary skill in the art is used to form the passageway. Although the osmotic device (1) is depicted with a single passageway (5), a device according to the present invention can comprise one or more passageways including two, three, four, five, six, seven, eight, nine, ten or more passageways. The one or more passageway/s are formed in any place of the delivery device. The maximum and minimum dimensions of the passageway are preferably as disclosed in US Patent 3,845,770 (AR 199,301).

The device of the present invention can, optionally, include an external coating comprising an active agent for immediate delivery to the environment of use. Useful materials for the external coating include poly(vinylpyrrolidone) (PVP), poly(ethylene glycol) (PEG), hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose, sodium carboxymethyl cellulose, dimethylaminoethyl methalcrylate-methalcrylate acid ester copolymer, soluble polysaccharide gums such as carrageenan, tragacanth, pectin, guar, combinations thereof and other such materials known by those of ordinary skill in the art. The external layer is dissolved, eroded or completely removed in the environment of use and provides an

immediate delivery of the active agent to the environment of use. The active agent comprises about 0.1 to 99.9% by weight of the external coating.

The layer (3) depicted in Figure 1-a includes a composition comprising an active agent and optionally other materials as discussed herein. The quantity of active agent may vary between 0.10 and 99.9% by weight of the layer (3). The preferred amount of active agent in the layer (3) may vary according to the active agent employed.

Osmotically effective compounds, such as osmotic agents or osmagents, that are capable of being totally or partially solubilized in the fluid may be added to the layer (3). Osmagents or osmotically effective compounds are generally soluble in the fluid that enters into the device through the wall (4) creating an osmotic pressure gradient across the wall. The fluid and components of the layer (3) will generally form a solution or suspension comprising the active agent to be delivered. Exemplary osmagents include high or low molecular weight compounds, organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials known to those of ordinary skill in the art. Preferred osmagents include potassium chloride, sodium tartrate, glucose, mannitol, sodium acetate, sodium chloride, sodium sulfate, sodium citrate, potassium tartrate, sorbitol, sucrose and combinations thereof.

The layer (3) comprising the active agent can also comprise an osmopolymer such as the ones previously described for the core (2), preferably poly(alkylene oxide) and, more preferably, poly(ethylene oxide) with an average molecular weight between about 100,000 and 8,000,000.

The delivery device of the invention advantageously requires lower amounts of osmagent, osmopolymer or osmotically effective agent to deliver an active substance than is required by related osmotic devices containing the same amount of active substance. Accordingly, the present delivery device contains a higher relative loading of active substance than other comparable osmotic devices containing the same absolute amount of

active substance, and is generally smaller and lighter than such other devices. In preferred embodiments, the percentage of active substance present in the entire device ranges from about 0.1% to about 99% with respect to the total weight of the device.

The delivery device of the invention can also comprise adsorbents, acidifying agents, alkalizing agents, antioxidants, buffering agents, colorants, flavorants, sweetening agents, antiadherents, binders, diluents, direct compression excipients, disintegrants, tablet glidants, tablet or capsule opaquants and/or tablet polishing agents.

As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, and trolamine and others known to those of ordinary skill in the art.

As used herein, the term "acidifying agent" is intended to mean a compound used to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, amino acid, citric acid, fumaric acid and other alpha hydroxy acids, such as hydrochloric acid, ascorbic acid, and nitric acid and others known to those of ordinary skill in the art.

As used herein, the term "adsorbent" is intended to mean an agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means. Such compounds include, by way of example and without limitation, powdered and activated charcoal and other such materials known to those of ordinary skill in the art.

As used herein, the term "antioxidant" is intended to mean an agent who inhibits oxidation and is thus used to prevent the deterioration of preparations by the oxidative process. Such compounds include, by way of example and without limitation, ascorbic acid, ascorbic palmitate, Vitamin E, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metalbisulfite and other such materials known to those of ordinary skill in the art.

As used herein, the term "buffering agent" is intended to mean a compound used to resist a change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such materials known to those of ordinary skill in the art.

As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

As used herein, the expression "antiadherents" is intended to mean agents that prevent the sticking of tablet formulation ingredients to the punches and dies in a tableting machine during production. Such compounds include, by way of example and without limitation, magnesium stearate, calcium stearate, talc, glyceryl behenate, poly(ethylene glycol), hydrogenated vegetable oil, mineral oil, stearic acid, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "binders" is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch, combinations thereof and other materials known to those of ordinary skill in the art.

When needed, other binders may also be included in the present osmotic device. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and and other such materials known to those of ordinary skill in the art.

As used herein, the term "diluent" or "filler" is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "tablet direct compression excipient" is intended to mean a compound used in direct compression tablet formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate (e.g. Ditab™), microcrystalline cellulose, direct compression lactose (e.g. Tablettose™, Lactose DT) , combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "glidant" is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "lubricant" is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "tablet/capsule opaquant" is intended to mean a compound used to used in tablet coatings or capsules providing useful opacity which can aid the stability to the light in case of sensitive agents. It may be used alone or in combination with a colorant. Such compounds include, by way of example and without limitation, titanium dioxide and other such materials known to those of ordinary skill in the art.

As used herein, the term "tablet polishing agent" is intended to mean a compound used to impart brightness to the surface of the coated tablets. Such compounds include, by

way of example and without limitation, carnauba wax, white wax, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "tablet disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starches thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g. Avicel™), carboxymethylcellulose calcium, cellulose polyacrylin potassium (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "colorant" is intended to mean a compound used to impart color to pharmaceutical preparations. Such compounds include, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, and iron oxide (black, red, yellow), other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, combinations thereof and other such materials known to those of ordinary skill in the art.

As used herein, the term "flavorant" is intended to mean a compound used to impart a pleasant flavor and often odor to a pharmaceutical preparation. Exemplary flavoring agents or flavorants include synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may also include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Other useful flavors include vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors, which have been found to be particularly useful, include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the desired organoleptic effect. Flavors will be present in any

amount as desired by the artisan of ordinary skill in the art. Particularly preferred flavors are the grape and cherry flavors and citrus flavors such as orange.

The delivery device of the invention can also include oils such as fixed oils, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids such as oleic acid, stearic acid and isostearic acid; and fatty acid esters such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. The device can also include alcohol such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; glycerol ketals such as 2,2-dimethyl-1, 3-dioxolane-4-methanol; ethers such as poly (ethyleneglycol) 450; petroleum hydrocarbons such as mineral oil and petrolatum; water; mixtures thereof; or a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

Soaps and synthetic detergents may be employed as surfactants and as vehicles for detergent compositions. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents such as dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents such as alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents such as fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; amphoteric detergents such as alkyl β-aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

Various other components, not otherwise listed above, can be added to the present formulation to provide a device with a desired release profile. Such components include, by way of example and without limitation, glycerylmonostearate, nylon, cellulose acetate butyrate, d,l-poly (lactic acid), 1,6-hexanediamine, diethylenetriamine, starches, derivatized starches, acetylated monoglycerides, gelatin coacervates, poly(styrene-maleic acid) copolymer, glycowax, castor wax, stearyl alcohol, glycerol palmitostearate, poly ethylene, poly(vinyl acetate), poly(vinyl chloride), 1,3-butylene-glycoldimethacrylate, ethyleneglycol-dimethacrylate and methacrylate hydrogels.

It should be understood that the compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named

herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

Active agents preferably include physiologically or pharmacologically active substances that produce a systemic or localized effect or effects on animals and human beings. Active agents also include pesticides, herbicides, insecticides, antioxidants, plant growth instigators, sterilization agents, catalysts, chemical reagents, food products, nutrients, cosmetics, vitamins, sterility inhibitors, fertility instigators, microorganisms, flavoring agents, sweeteners, cleansing agents and other such compounds for pharmaceutical, veterinary, horticultural, household, food, culinary, agricultural, cosmetic, industrial, cleaning, confectionery and flavoring applications. The active agent can be present in its neutral, ionic, salt, basic, acidic, natural, synthetic, diastereometric, isomeric, enantiomerically pure, racemic, hydrate, chelate, derivative, analog, or other common form.

When the active agent is a therapeutic compound, exemplary therapeutic compounds include antibiotics, antihistamines and decongestants, antiinflammatory agents, antiparasitics, antivirals, local anesthetics, antifungal agents, amoebicidal agents, trichomonocidal agents, analgesics, antiarthrits agents, anthiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, neuroleptics, antihypertensives, antidepressants, hypnotics, sedatives, anxyolitic energizers, anti-convulsants, antiparkinson agents, muscle relaxant agents, antimalarials, hormonal agents, contraceptives, sympathomimetics, diuretics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents and cardiovascular drugs.

Representative antibacterial substances include, for example, penicillins: penicillin G and V, penicillinase-resistant penicillin (methicillin, nafcillin, oxacilin, cloxacilin and dicloxacillin), and aminopenicillins: ampicillin, amoxicillin, cyclacillin; carboxy and ureidopenicillines such as carbenicillin, ticarcillin, azlocillin, mezlocillin and piperacilllin; cephalosporins such as the first-generation cephalosporins such as cephalotin, cephalexin, cefazolin, second generation cephalosporins such as cefoxitin, cefaclor, cefuroxime, and third generation cephalosporins such as cefotaxime, ceftriaxone,ceftazidime; beta-lactam

antibiotics such as imipenem, aztreonam; sulfonamides such as sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfasalazine and trimethropim-sulfamethoxazole; tetracyclines such as oxytetracycline, methacycline, chlorotetracycline and doxycycline; chloramphenicol, erythromycin, lincomycin, clindamycin, vancomycin, bacitracin; aminoglycoside antiobiotics such as streptomycin, gentamicin, tobramycin, amikacin, kanamycin and neomycin; and quinolones such as nalidixic acid, norfloxacin, ciprofloxacin, cinoxacin, ofloxacin, enoxacin, lomefloxacin, amifloxacin and pefloxacin.

Representative antiparasitic compounds include anthelmintics such as ivermectin, mebendazole, albendazole, piperazine, praziquantel, thiabendazole, and dapsone. Representative anti-malarial compounds include chloroquine and its congeners, diaminopyrimidines, mefloquine, primaquine and pyrimethamine. Miscellaneous antiparasitic agents include 8-hydroxyquinolines, metronidazole, quinacrine and paromomycin.

Representative antiviral compounds include acyclovir, gancyclovir, pencyclovir, foscarnet, idoxuridine, trifluridine and vidarabine; anti-retroviral compunds such as zidovudine, didadosine, estavudine; and others such as interferon, amantadine and rivavirine.

Representative antineoplastics include nitrogen mustards such as mechlorethamine chlorambucil, cyclophosphamide; ethylenimines and methylmelamines such as triethylenemelamine, thiotepa, hexamethyl-melamine; alkyl sulfonates such as busulfan; nitrosureas such as carmustine (BCNU), lomustine; dacarbazine; folic acid analogs such as methotrexate; pyrimidine analogs such as fluorouracil, arabinoside cytisine; purine analogs such as mercaptopurine, azathiprine; vinca alkaloids such as vincristine, vinblastine, taxol; etoposide; antibiotics such as actinomycin D, daunorubicin, doxorubicin, bleomycin, mitomycin; cisplatin; hydroxyurea; procarbazine; aminoglutethimide; cisplatin and tamoxifen.

Representative anti-inflammatory and analgesic drugs include cortisone, hydrocortisone, prednisone, prednisolone, betamethasone, dexamethasone and fluorocortisone; salycilates such as salycilic acid, aspirin and diflunisal; pyrazolon derivates such as phenylbutazone and oxyphenbutazone; aminopyridines such as dipyrone,

paraaminophenol derivates such as acetaminophen and phenacetin, indomethacin and sulindac; fenamates such as mefenamic acid; tolmetin; propionic acid derivates such as ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen and indoprofen; piroxicam, and diclofenac. Representative opoid analgesics include morphine, codeine, meperidine and nalorphine.

Representative drugs used in the treatment of gout include colchicine, allopurinol, probenecid and sulphinpirazone.

Representative antihistamines and decongestants include the first generation compounds such as diphenhydramine, pirilamine, chlorpheniramine, brompheniramine, promethazine; and second-generation compounds such as astemizole, loratadine and terfenadine.

Representative sympathomimetic drugs include epinephrine, amphetamine, ephedrine and norepinephrine.

Representative antiasthmatic drugs include methylxanthines such as theophylline; from corticoids such as beclomethasone dipropionate, budesonide, flunisolide, prednisone; bronchodilators such as albuterol, salbutamol, salmetherol, terbutaline; antimuscharinic agents such as ipratopium bromide; and cromolyn sodium.

Representative local anesthetics include benzocaine, procaine, lidocaine, cocaine, tetracaine, bupivacaine and dibucaine.

Representative muscle relaxants and antispasmodic agents include baclofen, succinylcholine, dantrolene, carisoprodol, metaxalone, cyclobenzaprine, diazepan, mephensin, trihexylphenidyl and biperiden. Representative antiparkinson disease compounds include levodopa, carbidopa, benceracide, amantadine, bromocriptine and pergolide.

Representative antidepressant include tricyclic agents such as amitriptyline, imipramine, clomipramine, doxepine; monoamine oxidase inhibitors such as isocoboxazid, phenelzine and tranylcypromine; fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, bupropione and trazodone.

Representative anticonvulsants include hydantoins such as phenytoin, barbiturates and deoxy derivates such as phenobarbital and primidone; carbamazepine; ethosuximide, valproic acid; and benzodiacepines such as diazepam and clonazepam.

Representative antipsychotics include chlorpromazine, trifluoperazine, thioridazine, fluphenazine, perphenazine, haloperidol, loxapine, molindone, clozapine, pimozide, risperidone and lithium.

Representative hypnotics and sedatives include barbiturates such as pentobarbital sodium, phenobarbital, secobarbital, thiopental; benzodiazepines such as diazepam, alprazolam, chlordiazepoxide, clonazepam, lorazepam, oxazepam; buspirone, meprobamate, zolpidem and zoplicone.

Representative hypoglucemic agents include insulin, insulin zinc, isophane insulin, protamine zinc insuline and extended insulin zinc suspension; sulfonylureas such as tolbutamide, chlorpropamide, acetohexamide, glyburide, glipizide, glicazide; biguanides such as phenformin, metformin; ciglitazone, troglitazone, and acarbose.

Representative antidiuretics drugs include inhibitors of carbonic anhydrase such as acetazolamide, chortalidone, indapamine; benzothiadiazides such as chlorothiazide, hydrochlorothiazide; ethacrynic acid, furosemide, bumetanide; aldosterone antagonists such as spironolactone; triamtirene and amiloride.

Representative antihypertensive and cardiovascular drugs include inhibitors of the renin-angiotensin system such as enalapril, lisinopril, ramipril, captopril, perindopril, trandolapril; angiotensin II receptors antagonists such as losartan; calcium channel blockers: nifedipine, amlodipine, nitrendipine, nimodipine, diltiazem, verapamil; simpathocolitic agents; adrenergic antagonists; atenolol, propanolol, nadolol, sotalol, timolol, metropolol, acebutolol, carvedilol; adrenergic agonists; prazosin, fentolamine; centrally acting agents such as methyldopa, clonidine, guanfacine, reserpine; direct arterial and venous vasodilators such as sodium nitroprusside, nitroglicerin, isosorbide 5-mononitrate, isosorbide dinitrate; antiarrithmic agents such as quinidine, procainamide, phenytoin, lidocaine, mexiletine, propafenone, flecainide, encainide, propranolol, acebutolol, amiodarone, sotalol, verapamil and diltiazem; digitalis; and cardiac glycosides such as digoxine, digitoxine, amrinone, and milrinone.

Representative anticoagulants include heparin, dicoumarol; thrombolytic agents such as streptokinase, tissue plasminogen activator (t-PA) urokinase and antiplatelet drugs such as dipyridamole, ticlopidine, and sulfinpyrazone.

Representative prokynetic gastrointestinal drugs include cisapride, domperidone, and metoclopramide.

Representative anti-spasmodic and muscle contractants include atropine, scopolamine, methoescopolamine and oxyphenonium.

Representative steroidal drugs include prednisolone, cortisone, cortisol and triamcinolone; androgenic steroids such as methyltesterone, and fluoxmesterone; estrogenic steroids such as 17β-estradiol, α-estradiol, estriol, α-estradiol 3 benzoate, and 17-ethynylestradiol-3-methyl ether; and progestational steroids such as progesterone, 19-nor-pregn-4-ene-3,20-dione, 17-hydroxy-19-nor-17-α-pregn-5(10)-ene-20-yn-3-one, 17α-ethynyl-17-hydroxy-5(10)-estren-3-one, and 9β, 10α-pregna-4,6-diene-3,20-dione.

Representative ophthalmic agents include pilocarpine, pilocarpine salts such as pilocarpine nitrate, pilocarpine hydrochloride, dichlophenamide, atropine, atropine sulfate, scopolamine and eserine salicylate.

Representative nutritional agents include ascorbic acid, niacin, nicotinamide, folic acid, choline biotin, panthothenic acid, and vitamin B12, essential amino acids, and essential fats.

Representative electrolytes include calcium gluconate, calcium lactate, potassium chloride, potassium sulfate, sodium chloride, sodium fluoride, ferrous lactate, ferrous gluconate, ferrous sulfate, ferrous fumarate and sodium lactate.

The above-mentioned list should not be considered exhaustive and is merely exemplary of the many embodiments considered within the scope of the invention. Many other active compounds can be administered with the device of the present invention.

The therapeutic compound(s) contained within the present device can be formulated as its pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the therapeutic compound is modified by reacting it with an acid or base as needed to form an ionically bound pair. Examples of pharmaceutically acceptable salts include conventional non-toxic

salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Suitable non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and others known to those of ordinary skill in the art. The salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and others known to those of ordinary skill in the art. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent therapeutic compound which contains a basic or acidic moiety by conventional chemical methods. Lists of other suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th. ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the relevant disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with tissues of human beings and animals and without excessive toxicity, irritation, allergic response, or any other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B12, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins and can include thiamin pyrophosphates (TPP), flavin mononucleotide (FMN), and flavin adenine dinucleotive (FAD). Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Coenzyme A (CoA), pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B12, lipolysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, carnitine, and alpha, beta, and gamma carotene.

As used in this disclosure, the term "mineral" refers to inorganic substances, metals, and the like required in the human diet. Thus, the term "mineral" as used herein includes, without limitation, calcium, iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium, mixtures thereof and others known to those of ordinary skill in the art.

The term "dietary supplement" as used herein means a substance, which has an appreciable nutritional effect when, administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, and fish oils, amino-acids, proteins, plant extracts, plant powder, herbs, herbal extracts and powders, vitamins, minerals, combinations thereof and others known to those of ordinary skill in the art. As will be appreciated, essentially any dietary supplement may be incorporated into the present osmotic device.

The amount of therapeutic compound incorporated in each device of the invention will be at least one or more dosage form and can be selected according to known principles of pharmacy. An effective amount of therapeutic compound is specifically contemplated. By the term "effective amount", it is understood that, with respect to, for example, pharmaceuticals, a pharmaceutically effective amount is contemplated. A pharmaceutically effective amount is the amount or quantity of a drug or pharmaceutically active substance which is enough for the required or desired therapeutic response, or in other words, the amount, which is sufficient to elicit an appreciable biological response when, administered to a patient. The appreciable biological response may occur as a result of administration of single or multiple unit doses of an active substance. Depending upon the active substance used and upon the amount of active substance present in a particular device according to the invention, a unit dose may comprise one or more such devices. As used with reference to a vitamin or mineral, the term "effective amount" means an amount at least about 10% of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient. For example, if an intended ingredient were vitamin C, then an effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

For nasal administration of therapeutic compounds, the device of the invention may be included in a paste, cream or ointment containing the appropriate solvents (such as water, aqueous, nonaqueous, polar, apolar, hydrophobic, hydrophilic and/or combinations thereof) and optionally other compounds (stabilizers, perfumes, antimicrobial agents, antioxidants, pH modifiers, surfactants and/or bioavailability modifiers). Bioavailability enhancers such as alcohols or other compounds that enhance the penetration of the therapeutic compound from the pharmaceutical formulation into the nasal mucosa may be needed to prepare suitable formulations for nasal administration.

For oral, buccal, and sublingual administration, the delivery device may be in the form of a caplet or tablet. For rectal administration, the osmotic device can be included in a suppository or tablet for release of a therapeutic compound into the intestines, sigmoid flexure and/or rectum. For cutaneous, subcutaneous, otic, intraperitoneal, ophthalmic and implant applications, the device is a solid dosage form adapted for such application and is preferably a tablet.

The device of the invention can be prepared according to the methods disclosed herein or those well known in the art. For example, according to a preferred process, the hydrophilic polymer or a mixture thereof is mixed with suitable excipients in solid form, is then moistened and sieved through a screen and dried for several hours in a convection oven. The dried granulate is then screened and mixed with other suitable excipients and the homogeneous mixture is subsequently compressed to form 4 to 10 mm diameter expandable placebo cores. A mixture comprising an active agent and a suitable excipient is then compressed over the core (2) to form 6 to 12 mm diameter uncoated tablets. Uncoated tablets are then covered preferably with a mixture of selected polymers that constitute the wall (4). Subsequently, the wall (4) is perforated at any location with a laser, drill or other mechanical means known to those of ordinary skill in the art. Optionally, the tablets may be further coated with an external film comprising an active agent for immediate or sustained delivery to the environment of use.

If desired, the device of the invention can be coated with a finish coating as is commonly done in the art to provide the desired shine, color, taste or other aesthetic

characteristics. Materials suitable for preparing the finish coating are well known to those of ordinary skill in the art.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments included within the scope of the present invention. The methods described herein can be followed to prepare delivery devices according to the invention.

EXAMPLE 1

Biconvex-shaped expandable cores about 7.0 mm in diameter were prepared without active agent as follows. 20.85 g of lactose monohydrate, 18.25 g of hydroxypropyl methylcellulose (HPMC; 2208 type; Dow Chemical U.S.A.); 1.8 g of poly(ethylene oxide) (4,000,000 molecular weight), 2.15 g of poly(vinylpyrrolidone), 0.30 g of red ferric oxide, and 0.45 g of silicon dioxide were mixed then sieved through a 40-mesh screen. Alcohol (96°, 30 ml) was slowly added to the dry blend until a wet blend was achieved. The wet blend was then sieved through a 10-mesh screen and the granular mass obtained was dried for several hours at 45°C in a convection oven. The dried granulate was then sieved through a 20-mesh screen. The sieved granulate was mixed with 0.75 g of magnesium stearate and 0.45 g of silicon dioxide (both having been previously sieved through a 60-mesh screen) and then mixed in a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed to form biconvex cores, which individually weighed 90.0 mg.

A first layer comprising the active agent was prepared as follows 20.75 g of cisapride monohydrate, 28.15 g of microcrystalline cellulose, 37.50 g. of sodium chloride, 45.00 g of poly(ethylene oxide) (200,000 molecular weight), 0.37 g of colloidal silicon dioxide and 15.75 g of poly(vinylpyrrolidone) were mixed and then sieved through a 40-mesh screen. The sieved mixture was then granulated with alcohol (96°,40 ml having 0.85 g of polysorbate 20 previously dissolved in it). All the ingredients were mixed for a few additional minutes. The granular mass was then dried for several hours at 45°C in a convection oven. Dried granulate was then sieved through a 20 mesh screen. The sieved mixture was mixed with 1.25 g of magnesium stearate and 0.38 g of colloidal silicon dioxide (both previously sieved through a 60 mesh screen) in a V-blender for 5 minutes to

form a homogeneous drug-containing composition. The drug-containing composition was compressed about the previously formed expandable cores to form biconvex uncoated cores, about 9.25 mm in diameter, each weighing about 390 mg.

A wall for covering the uncoated cores was prepared as follows. A polymeric suspension was prepared by dissolving 27.36 g of cellulose acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 6.84 g of ammonium methacrylate copolymer (Eudragit™ RS 100, Röhm Pharma) and, 5 weight percent poly(ethylene glycol), in a mixture of methylene chloride-methyl alcohol 80:20 v/v. The polymeric suspension was then sprayed onto the uncoated tablets to form coated tablets having a wall weighing about 31.63 mg. Two 0.75-mm holes were drilled through the coating in both faces of the device to form a delivery device according to the invention.

Figure 2 discloses the results of a drug delivery assay performed on the delivery device in a USP type 3 Apparatus, in distilled water (250 ml, 30 DPM at 37°C). The release data are summarized in the table below.

Hours	Accumulative Amount Released (%)
1	2.4
3	27.8
6	64.8
9	85.6
12	91.7
15	93.3
21	94.0
24	94.7

EXAMPLE 2

Biconvex-shaped cores of 8.0 mm in diameter were prepared without active agent as follows. 21.50 g of hydroxypropyl methylcellulose (HPMC; 2208 type), 23.75 g of poly(ethylene oxide) (300,000 molecular weight), 2.71 g of poly(vinylpyrrolidone), 0.35 g of red ferric oxide, and 0.53 g of silicon dioxide were mixed and sieved through a 40-mesh screen. Then, alcohol (96°; 40 ml) was slowly added to the dry blend to form a wet blend which was sieved through a 10-mesh screen. The resulting granular mass was dried for

several hours at 45°C in a convection oven, and then sieved through a 20-mesh screen. The granulate was mixed with 0.88 g of magnesium stearate and 0.53 g of silicon dioxide (both after having been sieved through a 60 mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed to form biconvex cores, which weighed about 100. mg each.

A first layer comprising the active agent was prepared as follows. 16.50 g of micronized nifedipine, 15.00 g of microcrystalline cellulose, 32.05 g of sodium chloride, 37.50 g of poly(ethylene oxide) (200,000 molecular weight), 0.75 g of colloidal silicon dioxide and 19.25 g of poly(vinylpyrrolidone) were mixed and sieved through a 40 mesh screen. The sieved mixture was granulated with alcohol (96°; 35 having 0.70 g of polysorbate 20 previously dissolved in it). All the ingredients were mixed for a few additional minutes. The granular mass was dried for several hours at 45°C in a convection oven, and the dried granulate was sieved through a 20-mesh screen. The sieved blend was then mixed with 1.75 g of magnesium stearate and 0.75 g of colloidal silicon dioxide (both having been previously sieved through a 60-mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed about the expandable cores to form biconvex dosage units of about 10 mm in diameter to form the coated device core. The average weight of the cores was about 360 mg.

A wall surrounding the uncoated core was prepared as follows. A polymer suspension was prepared by dissolving 13.3 mg of cellulose acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 13.3 mg of cellulose acetate (average molecular weight 38,000, acetyl content 39.8% by weight CA), 6.65 g of ammonium methacrylate copolymer (Eudragit™ RS 100, Röhm Pharma) and 1.75 g of poly(ethylene glycol), in a mixture of methylene chloride-methyl alcohol 80:20 v/v (493/123 ml). The polymeric mixture was sprayed onto the dosage units to form coated tablets each having a wall weighing about 35 mg. Two 0.75-mm holes were then drilled through the wall, one on each face of the device.

Figure 3 depicts the release profile for the tablets of this example. The release profile was determined in a USP type 3 Apparatus, in distilled water (250 ml., 30 DPM at 37°C). The actual release data obtained are summarized below.

Hours	Accumulative Amount Released (%)
1	0.4
3	13.4
6	42.6
9	63.6
12	77.7
15	87.9
21	94.5
24	94.8

EXAMPLE 3

Biconvex-shaped expandable cores about 7 mm in diameter were prepared as follows. 20.85 g of lactose monohydrate, 18.25 g of hydroxypropyl methylcellulose (HPMC, 2208 type), 1.8 g of poly(ethylene oxide) (4,000,000 molecular weight), 2.15 g of poly(vinylpyrrolidone), 0.30 g of red ferric oxide as coloring agent and 0.45 g of silicon dioxide were mixed, and the mix was sieved through a 40-mesh screen. Then, alcohol (96°; 30 ml) was slowly added to the dry blend until a wet blend was achieved. The wet blend was then sieved through a 10 mesh screen and the resulting granulate was dried in a convection oven for several hours. The dried granulate was sieved through a 20-mesh screen and mixed with 0.75 g magnesium stearate and 0.45 g silicon dioxide (both having been previously sieved through a 60-mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed to form biconvex cores each weighing about 90 mg.

A first layer containing the active agent was prepared as follows. 42.43 g of venlafaxine hydrochloride, 25.22 g of microcrystalline cellulose, 37.5 g of sodium chloride, 45 g of poly(ethylene oxide) (200,000 molecular weight), 0.35 g of colloidal silicon dioxide and 12.00 g of poly(vinylpyrrolidone) were mixed. The blend was sieved through a 40-mesh screen. This mixture was granulated with alcohol (96°; 40 ml, having 0.85 g of polysorbate 20 previously dissolved in it). All the ingredients were mixed for a few additional minutes. The granular mass was dried for several hours at 45°C in a convection oven. Then the dry granulate was sieved through a 20-mesh screen. The sieved

blend was mixed with 1.25 g of magnesium stearate and 0.40 g of colloidal silicon dioxide (having both been previously sieved through a 60 mesh screen) in a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed about the expandable cores to form biconvex-shaped uncoated cores about 9.25 mm in diameter, each weighing about 330 mg.

A wall for covering the uncoated cores was prepared as follows. A polymer suspension was prepared by dissolving 27.36 g of cellulose acetate (average molecular weight 40,000, acetyl content 32% by weight CA), 6.84 g of ammonium methacrylate copolymer (Eudragit™ RS 100, Röhm Pharma) and 1.84 g of poly(ethylene glycol), in a methylene chloride-methyl alcohol mixture of about 80:20 v/v (493 ml/ 123 ml). This polymer mixture was sprayed onto the uncoated cores to form coated cores, each having a wall weighing about 32.3 mg. Two 0.75-mm holes were drilled through the coating on both faces of the device.

Figure 4 depicts the release profile obtained with the device of this example. The release profile was determined in a USP Type 2 Apparatus, in distilled water, 800 ml, 100 rpm at 37°C. The actual release data obtained are summarized below.

Hours	Accumulated Amount Dissolved (%)
1	4.7
3	19.1
6	48.5
9	66.9
12	73.3
15	75.5
21	78.5
24	80.9

EXAMPLE 4

DEVICE HAVING A RAPID RELEASE EXTERNAL COATING CONTAINING DRUG.

A drug dosage form adapted, designed and shaped as an osmotic delivery system, containing two layers surrounding a central core, including active agent and hydrophilic

polymer in the first layer and, cellulose acetate and ammonium methacrylate copolymer in the second layer, and having a rapid release external coating was manufactured as follows.

Round, biconvex-shaped cores of 7.0 mm in diameter were prepared without active agent as follows: 20.85 g of lactose monohydrate as filling material; 18.25 g of hydroxypropyl methylcellulose (HPMC of 2208 type) as hydrophilic polymer; 1.8 g of polyethylene oxide having a 4,000,000 molecular weight; 2.15 g of poly(vinylpyrrolidone); 0.30 g of red ferric oxide as coloring agent and 0.45 g of silicon dioxide were mixed and the mix was passed through a 40-mesh screen. Then, alcohol 96° was slowly added to the dry blend until a wet blend was achieved. The wet blend was passed through a 10-mesh screen and the granular mass was dried for several hours at 45°C in a convection oven. Then the dry granulate was passed through a 20-mesh screen. The screened granulation was mixed with 0.75 g of magnesium stearate and 0.45 g of silicon dioxide (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed to form biconvex cores which individually weighed 90.0 mg.

The first layer was prepared containing the active agent as follows: 20.75 g of Cisapride monohydrate; 28.15 g of microcrystalline cellulose; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal silicon dioxide and 15.75 g of poly vinylpyrrolidone were mixed and the mix was passed through a 40-mesh screen. This mixture was granulated with alcohol 96° together with 0.85 g of polysorbate 20 previously dissolved in it and all the ingredients were mixed for a few additional minutes. The granular mass was dried for several hours at 45°C in a convection oven. Then the dry granulate was passed through a 20-mesh screen.

The screened blend was mixed with 1.25 g of magnesium stearate and 0.38 g of colloidal silicon dioxide (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed surrounding the central core which was obtained in the first part, obtaining 9.25-mm diameter biconvex tablets. The average weight of the cores was 390.0 mg.

The second layer was formed by the above tablets which were then coated with a semipermeable wall. A polymer suspension was prepared dissolving 76 weight percent of

cellulose acetate; 19 weight percent of ammonium methacrylate copolymer (Eudragit RS 100, Röhn Pharma) and, 5 weight percent polyethylene glycol 400, with the total weight percent equal to 100, in a mixture of methylene chloride-methyl alcohol 80:20 v/v (volume/volume). This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets whose membrane coating weighed 31.63 mg. A 0.75-mm hole was drilled through the coating in both faces of the device.

A rapid release external coating was prepared by mixing 33.48 g of ranitidine HCl, 131.02 g of microcrystalline cellulose, 25.00 g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of colloidal silicon dioxide. The mixture was blended to homogenize; then, 2.00 g of magnesium stearate was added as lubricant. This blend was tabletted to 800 mg – 1000 mg/core and hardness of 8 – 12 kP with flat faced, 13.0-mm diameter punches. The slugs were milled by passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline cellulose, 0.50 g of colloidal silicon dioxide, 5.00 g of croscarmellose sodium and 2.00 g of magnesium stearate. This final blend was compressed over the film-coated tablets by compression using biconcaves, 13.0-mm diameter punches. Coating weight: 332 mg. Hardness from 10 to 15 kp.

The final coating was prepared by mixing 10,89 g of hydroxypropyl methylcellulose 2910, 3.10 g of polyethylene glycol 6000, 3.99 g of titanum dioxide, 22.00 mg of Aluminum Lake Red Ponceau in a mixture of 280 ml of methylene chloride and 120 ml of alcohol 96°. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets whose membrane coating weighed 18 mg approximately.

EXAMPLE 5

DEVICE HAVING A CONTROLLED, SLOW OR DELAYED RELEASE EXTERNAL COATING CONTAINING DRUG.

A drug dosage form adapted, designed and shaped as an osmotic delivery system, containing two layers surrounding a central core, including active agent and hydrophilic polymer in the first layer and, cellulose acetate and ammonium methacrylate copolymer in

the second layer, and having a delayed release external coating was manufactured as follows:

Round, biconvex-shaped cores of 7.0 mm in diameter were prepared without active agent as follows: 20.85 g of lactose monohydrate as filling material; 18.25 g of hydroxypropyl methylcellulose (HPMC of 2208 type) as hydrophilic polymer; 1.8 g of polyethylene oxide having a 4,000,000 molecular weight; 2.15 g of poly(vinylpyrrolidone); 0.30 g of red ferric oxide as coloring agent and 0.45 g of silicon dioxide were mixed and the mix was passed through a 40-mesh screen. Then, alcohol 96° was slowly added to the dry blend until a wet blend was achieved. The wet blend was passed through a 10-mesh screen and the granular mass was dried for several hours at 45°C in a convection oven. Then the dry granulate was passed through a 20-mesh screen. The screened granulation was mixed with 0.75 g of magnesium stearate and 0.45 g of silicon dioxide (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed to form biconvex cores that individually weighed 90.0 mg.

The first layer was prepared containing the active agent as follows: 20.75 g of cisapride monohydrate; 28.15 g of microcrystalline cellulose; 37.50 g of sodium chloride; 45.00 g of polyethylene oxide having a 200,000 molecular weight; 0.37 g of colloidal silicon dioxide and 15.75 g of poly(vinylpyrrolidone) were mixed and the mixture was passed through a 40-mesh screen. This mixture was granulated with alcohol 96° together with 0.85 g of polysorbate 20 previously dissolved in it and all the ingredients were mixed for a few additional minutes. The granular mass was dried for several hours at 45°C in a convection oven. Then the dry granulate was passed through a 20-mesh screen. The screened blend was mixed with 1.25 g of magnesium stearate and 0.38 g of colloidal silicon dioxide (both previously passed through a 60-mesh screen) and placed into a V-blender for 5 minutes. The homogeneous mixture was subsequently compressed about the central core which were obtained in the first part, to form 9.25-mm diameter biconvex tablets. The average weight of the cores was 390.0 mg.

The second layer was formed by the above tablets which were then coated with a semipermeable wall. A polymer suspension was prepared dissolving 76 weight percent of

cellulose acetate; 19 weight percent of ammonium methacrylate copolymer (Eudragit RS 100, Röhn Pharma) and, 5 weight percent polyethylene glycol 400, with the total weight percent equal to 100, in a mixture of methylene chloride-methyl alcohol 80:20 v/v (volume/volume). This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets whose membrane coating weighed 31.63 mg. A 0.75-mm hole was drilled through the coating in both faces of the device.

A delayed release external coating was prepared by mixing 33.48 g of ranitidine HCl, 131.02 g of microcrystalline cellulose, 25.00 g of povidone, 8.00 g of polyethylene glycol 6000, 1.70 g of polyethylene glycol 400 and 1.00 g of colloidal silicon dioxide. The mixture was blended to homogenize; then, 2.00 g of magnesium stearate was added as lubricant. This blend was tabletted to form 800 mg – 1000 mg cores having a hardness of 8 – 12 kP with flat faced, 13.0-mm diameter punches. The slugs were milled by passing through a standard USP 20-mesh screen and were blended with 122.30 g of microcrystalline cellulose, 0.50 g of colloidal silicon dioxide, 5.00 g of croscarmellose sodium and 2.00 g of magnesium stearate. This final blend was compressed over the film-coated tablets by compression using biconcaves, 13.0-mm diameter punches. Coating weight: 332 mg. Hardness from 10 to 15 kp.

The final coating was prepared by mixing 21.80 g of methacrylic acid copolymer, USP Type A, 1.45 g of polyethylene glycol 6000, 4.60 g of titanum dioxide, 7.00 g of talc and 0.15 mg of Red Ferric Oxide in 780 ml of isopropyl alcohol.. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 35 mg approximately.

The above is a detailed description of particular embodiments of the invention. It is recognized that departures from the disclosed embodiments may be made within the scope of the invention and that obvious modifications will occur to a person skilled in the art. Those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed herein and still obtain a like or similar result without departing from the spirit and scope of the invention. All of the

embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

CLAIMS

We claim the following:

1. A device for the controlled delivery of active agents to an environment of use, wherein the device comprises:

a) a core located approximately at the center of the device and comprising at least one expandable hydrophilic polymer and, optionally, an osmagent, said core being able to absorb fluids from the environment of use;

b) a composition immediately surrounding the core comprising at least one active substance and, optionally, one or more of an osmagent and an osmopolymer;

c) a membrane immediately surrounding the composition and comprising a mixture of a cellulose acylate, a poly(methacrylate) copolymer salt and a plasticizer, wherein the membrane permits delivery of the at least one active substance through a combination of diffusion and osmotic pumping; and

d) one or more preformed passageways and plural micropores in the membrane that communicate the composition with the outside of the device.

2. A device according to claim 1, wherein the expandable hydrophilic polymer is one or more of hydroxypropyl methylcellulose, alkylcelullose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof.

3. A device according to claim 1, wherein the membrane comprises about 1 to 99 weight percent of one or more cellulose esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salt and about 15 to 0.5 weight percent of one or more plasticizers.

4. A device according to claim 3, wherein the cellulose ester is selected form the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

5. A device according to claim 3, wherein the poly(methacrylate) copolymer salt is poly(ammonium methacrylate) copolymer.

6. A device according to claim 3, wherein the plasticizer is selected from the group consisting of acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, poly(ethylene glycol), triacetin, propylene glycol, dibutyl

phthalate, diethyl phthalate, dipropyl phthalate, dimethyl phthalate, dioctyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, and coconut oil.

7. A device according to claim 1, wherein the active agent is one of a biologically active agent, pharmacologically active agent, medicine, nutrient, food product, vitamin, insecticide, pesticide, herbicide, microbicide, algaecide, fungicide, grow regulating substance, parasiticide, sterilant, fertility promoter, biocide, rodenticide, disinfectant, plant growth promoter, preservative, fertility inhibitor, deodorant, catalysts, food supplement and cosmetic.

8. A device according to claim 1, wherein a slightly soluble or insoluble active substance is delivered predominantly through the at least one passageway and a soluble or sparingly soluble active substance is delivered predominantly through the plural micropores.

9. A device according to claim 1 further comprising an external coat comprising a second active substance for the immediate, rapid, controlled or delayed release of the second active substance, wherein the external coat surrounds at least a portion of the membrane.

10. A device according to claim 1, wherein the active substance is slightly soluble or insoluble in a fluid from the environment of use, and the active substance is delivered predominantly through the one or more preformed passageways.

11. A device according to claim 9, wherein the active substance is delivered at an approximately zero order rate.

12. A device according to claim 1, wherein the active substance is at least sparingly soluble in a fluid from the environment of use, and a significant portion of the active substance is delivered through the micropores of the membrane.

13. A device according to claim 12, wherein the active substance is delivered at an approximately zero order rate.

14. A device for the controlled delivery of an active substance that to an environment of use wherein the active substance is one of very soluble, sparingly soluble, slightly soluble or insoluble in a fluid imbibed by the device from the environment of use, the device comprising:

a core expandable in a fluid from the environment of use, the core being approximately centrally located in the device;

a layer comprising the active substance in contact with and surrounding the core; and

a membrane in contact with and surrounding the layer and comprising at least one passageway made by mechanical means for delivery of the active substance by osmotic pumping and plural micropores for delivery of the active substance by diffusion.

15. The device of claim 14, wherein a slightly soluble or insoluble active substance is delivered predominantly through the at least one passageway.

16. The device of claim 14, wherein a significant portion of a very soluble or sparingly soluble active substance is delivered through the plural micropores.

17. The device of claim 14, wherein the mechanical means is at least one of a laser and a drill.

18. The device of claim 14, wherein the fluid is an aqueous fluid.

19. The device of claim 14, wherein the core comprises an expandable polymer.

20. The device of claim 19, wherein the expandable polymer is selected from the group consisting of hydroxypropyl methylcellulose, alkylcelullose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof.

21. The device of claim 14, wherein the layer further comprises at least one of an osmagent and an osmopolymer.

22. The device of claim 21, wherein the osmagent is selected from the group consisting of sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-monohydrate lactose, glucose and combinations thereof.

23. The device of claim 21, wherein the osmopolymer is selected from the group consisting of hydroxypropyl methylcellulose, alkylcellulose, hydroxyalkylcellulose, poly(alkylene oxide), or a combination thereof.

24. The device of claim 14, wherein the membrane comprises at least one cellulose ester, at least one poly(methacrylate) copolymer salt and at least one plasticizer.

25. The device of claim 24, wherein the at least one cellulose ester is independently selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

26. The device of claim 24, wherein the at least one poly(methacrylate) copolymer salt is a poly(ammonium methacrylate) copolymer.

27. The device of claim 24, wherein the at least one plasticizer is selected from the group consisting of acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, poly(ethylene glycol), triacetin, propylene glycol, dibutyl phthalate, diethyl phthalate, dipropyl phthalate, dimethyl phthalate, dioctyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, and coconut oil.

28. The device of claim 14, wherein the membrane comprises about 1 to 99% wt. of at least one cellulose ester, about 84 to 0.5% wt. of at least one poly(methacrylate) copolymer salt, and about 15 to 0.5% wt. of at least one plasticizer.

29. The device of claim 14 further comprising an external coat comprising a second active substance for the immediate, rapid, controlled or delayed release of the second active substance, wherein the external coat surrounds at least a portion of the membrane.

30. The device of claim 29, wherein the first and second active substances are the same.

31. The device of claim 29, wherein the first and second active substances are different.

32. A device according to claim 19, wherein the expandable core further comprises an osmagent.

33. A device according to claim 32, wherein the osmagent is selected from the group consisting of sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-monohydrate lactose, glucose and combinations thereof.

34. A device according to any one of claims 14-33, wherein the active substance is a therapeutic agent.

35. A device according to claim 14, wherein the device is adapted for one of oral, buccal, sublingual, rectal, anal, dermal, subdermal, cutaneous, subcutaneous, intraperitoneal, ophthalmic, otic and implant administration.

36. A device according to claim 14 further comprising one or more of an adsorbent, antioxidant, buffering agent, colorant, flavorant, sweetening agent, anti-adherent, binder, diluent, direct compression excipient, disintegrant, tablet glidant, tablet opaquant and tablet polishing agent.

37. A device according to claim 14, wherein the active substance is cisapride.

38. A device according to claim 14, wherein the active substance is nifedipine.

39. A device according to claim 14, wherein the active substance is venlafaxine.

AMENDED CLAIMS

[received by the International Bureau on 25 May 2001 (25.05.01); original claims 1-39 replaced by new claims 1-23 and 25-34 (4 pages)]

1. A device for the controlled delivery of active agents to an environment of use, wherein the device comprises:

a) a core located approximately at the center of the device and comprising at least one expandable hydrophilic polymer and, optionally, an osmagent, said core being able to absorb fluids from the environment of use;

b) a composition immediately surrounding the core comprising at least one active substance and, optionally, one or more of an osmagent and an osmopolymer;

c) a membrane immediately surrounding the composition and comprising a mixture of a cellulose acylate, a poly(methacrylate) copolymer salt and a plasticizer, wherein the membrane permits delivery of the at least one active substance through a combination of diffusion and osmotic pumping; and

d) one or more preformed passageways and plural micropores in the membrane that communicate the composition with the outside of the device.

2. A device according to claim 1, wherein the expandable hydrophilic polymer is one or more of hydroxypropyl methylcellulose, alkylcelullose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof.

3. A device according to claim 1, wherein the membrane comprises about 1 to 99 weight percent of one or more cellulose esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salt and about 15 to 0.5 weight percent of one or more plasticizers.

4. A device according to claim 3, wherein the cellulose ester is selected form the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

5. A device according to claim 3, wherein the poly(methacrylate) copolymer salt is poly(ammonium methacrylate) copolymer.

6. A device according to claim 3, wherein the plasticizer is selected from the group consisting of acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, poly(ethylene glycol), triacetin, propylene glycol, dibutyl

phthalate, diethyl phthalate, dipropyl phthalate, dimethyl phthalate, dioctyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, and coconut oil.

7. A device according to claim 1, wherein the active agent is one of a biologically active agent, pharmacologically active agent, medicine, nutrient, food product, vitamin, insecticide, pesticide, herbicide, microbicide, algaecide, fungicide, grow regulating substance, parasiticide, sterilant, fertility promoter, biocide, rodenticide, disinfectant, plant growth promoter, preservative, fertility inhibitor, deodorant, catalysts, food supplement and cosmetic.

8. A device according to claim 1, wherein a slightly soluble or insoluble active substance is delivered predominantly through the at least one passageway and a soluble or sparingly soluble active substance is delivered predominantly through the plural micropores.

9. A device according to claim 1 further comprising an external coat comprising a second active substance for the immediate, rapid, controlled or delayed release of the second active substance, wherein the external coat surrounds at least a portion of the membrane.

10. A device according to claim 1, wherein the active substance is slightly soluble or insoluble in a fluid from the environment of use, and the active substance is delivered predominantly through the one or more preformed passageways.

11. A device according to claim 9, wherein the active substance is delivered at an approximately zero order rate.

12. A device according to claim 1, wherein the active substance is at least sparingly soluble in a fluid from the environment of use, and a significant portion of the active substance is delivered through the micropores of the membrane.

13. A device according to claim 12, wherein the active substance is delivered at an approximately zero order rate.

14. A device for the controlled delivery of an active substance to an environment of use wherein the active substance is one of very soluble, sparingly soluble, slightly soluble or insoluble in a fluid imbibed by the device from the environment of use, the device comprising:

a core expandable in a fluid from the environment of use, the core being approximately centrally located in the device;

a layer comprising the active substance in contact with and completely surrounding the core; and

a membrane in contact with and completely surrounding the layer and comprising at least one passageway made by mechanical means for delivery of the active substance by osmotic pumping and plural micropores for delivery of the active substance by diffusion, wherein the membrane comprises about 1 to 99 weight percent of one or more cellulose esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salt and about 15 to 0.5 weight percent of one or more plasticizers.

15. The device of claim 14, wherein a slightly soluble or insoluble active substance is delivered predominantly through the at least one passageway.

16. The device of claim 14, wherein a significant portion of a very soluble or sparingly soluble active substance is delivered through the plural micropores.

17. The device of claim 14, wherein the mechanical means is at least one of a laser and a drill.

18. The device of claim 14, wherein the fluid is an aqueous fluid.

19. The device of claim 14, wherein the core comprises an expandable polymer.

20. The device of claim 19, wherein the expandable polymer is selected from the group consisting of hydroxypropyl methylcellulose, alkylcelullose, hydroxyalkylcellulose, poly(alkylene oxide), and combinations thereof.

21. The device of claim 14, wherein the layer further comprises at least one of an osmagent and an osmopolymer.

22. The device of claim 21, wherein the osmagent is selected from the group consisting of sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-monohydrate lactose, glucose and combinations thereof.

23. The device of claim 21, wherein the osmopolymer is selected from the group consisting of hydroxypropyl methylcellulose, alkylcellulose, hydroxyalkylcellulose, poly(alkylene oxide), or a combination thereof.

25. The device of claim 14, wherein the at least one cellulose ester is independently selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

26. The device of claim 14, wherein the at least one poly(methacrylate) copolymer salt is a poly(ammonium methacrylate) copolymer.

27. The device of claim 14, wherein the at least one plasticizer is selected from the group consisting of acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, poly(ethylene glycol), triacetin, propylene glycol, dibutyl phthalate, diethyl phthalate, dipropyl phthalate, dimethyl phthalate, dioctyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, and coconut oil.

29. The device of claim 14 further comprising an external coat comprising a second active substance for the immediate, rapid, controlled or delayed release of the second active substance, wherein the external coat surrounds at least a portion of the membrane.

30. The device of claim 29, wherein the first and second active substances are the same.

31. The device of claim 29, wherein the first and second active substances are different.

32. A device according to claim 19, wherein the expandable core further comprises an osmagent.

33. A device according to claim 32, wherein the osmagent is selected from the group consisting of sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-monohydrate lactose, glucose and combinations thereof.

34. A device according to any one of claims 14-23, 25-27 or 29-33, wherein the active substance is a therapeutic agent.

AMENDMENT AND STATEMENT UNDER ARTICLE 19

In response to the Notification of Transmittal of The International Search Report mailed 13 MARCH 2001, regarding the above-identified International Application, Applicants hereby submit the following amendment and statement.

Applicants hereby request correction of the name of one of the Applicants. The Notification incorrectly identifies the applicant as "LABORATORIES PHOENIX U.S.A., INC. However, the Request correctly identifies the applicant as "LABORATORIOS PHOENIX U.S.A., INC."

AMENDMENT

On page 8, in the last line of the table, replace "of" with -- or --.

Please amend the claims as follows:

14. A device for the controlled delivery of an active substance [that] to an environment of use wherein the active substance is one of very soluble, sparingly soluble, slightly soluble or insoluble in a fluid imbibed by the device from the environment of use, the device comprising:

a core expandable in a fluid from the environment of use, the core being approximately centrally located in the device;

a layer comprising the active substance in contact with and completely surrounding the core; and

a membrane in contact with and completely surrounding the layer and comprising at least one passageway made by mechanical means for delivery of the active substance by

osmotic pumping and plural micropores for delivery of the active substance by diffusion, wherein the membrane comprises about 1 to 99 weight percent of one or more cellulose esters, about 84 to 0.5 weight percent of one or more poly(methacrylate) copolymer salt and about 15 to 0.5 weight percent of one or more plasticizers.

Please cancel claim 24.

25. The device of claim [24] 14, wherein the at least one cellulose ester is independently selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

26. The device of claim [24] 14, wherein the at least one poly(methacrylate) copolymer salt is a poly(ammonium methacrylate) copolymer.

27. The device of claim [24] 14, wherein the at least one plasticizer is selected from the group consisting of acetyl triethyl citrate, acetyl tributyl citrate, triethyl citrate, acetylated monoglycerids, glycerol, poly(ethylene glycol), triacetin, propylene glycol, dibutyl phthalate, diethyl phthalate, dipropyl phthalate, dimethyl phthalate, dioctyl phthalate, dibutyl sebacate, dimethyl sebacate, castor oil, glycerol monostearate, and coconut oil.

Please cancel claim 28.

34. A device according to any one of claims 14-23, 25-27 or 29-33, wherein the active substance is a therapeutic agent.

STATEMENT

Claims 1-23, 25-27 and 29-39 are pending herein. Claim 24 has been canceled. Claims 25-27 have been amended to change their dependency from claim 24 to claim 14. Claim 28 has been canceled. Claim 34 has been amended to correct its dependency.

Claim 14 has been amended to include the subject matter of claim 28 and by further limiting the term "surrounding" as "completely surrounding". As noted in the attached copy of page 1173 of Webster's New Collegiate Dictionary (1977), the term "surrounding" means "to enclose on all sides; envelop". As detailed in the specification and as indicated in the drawings, the drug-containing layer completely surrounds the expandable core, and the membrane completely surrounds the drug-containing layer.

The specification has been amended to correct a typographical error in the last line of the table on page 8.

Substitute pages 8 and 38-41 are attached hereto.

U.S. Patents No. 4,693,886 to Ayer, No. 4,765,989 to Wong et al., and No. 4,859,470 to Guittard et al. all of Alza Corp. are denoted as "X" and "Y" references and as being relevant to claims of the application. In addition, U.S. Patent No. 5,004,614 to Staniforth of Forum Chemicals, Ltd. is denoted as a "Y" reference and as being relevant to claims 1-11, 14, 15, and 17-39. Insofar as it may apply to the present claims, Applicants respectfully disagree.

The Ayer patent discloses an osmotic device comprising an inert core, which serves as a carrier means for a drug-containing layer surrounding the core. The core is not made of an expandable material, i.e., a material that expands when exposed to an aqueous fluid. Ayer specifically states that the preferred inert core "lacks affinity for water, and it does not substantially absorb or imbibe aqueous type fluids" (Col. 5, lines 9-11). Moreover, the osmotic device of Ayer releases drug only by osmotic pumping. On the other hand, the expandable core is required by the presently claimed device, and, by virtue of its construction, the claimed device delivers drug by both osmotic pumping and diffusion.

The Wong et al. patent discloses an osmotic device comprising a bi-layered core surrounded by a drug-containing layer. The layers of the core are in stacked arrangement; therefore, the drug-containing layer does not completely surround the expandable layer. This type of device is limited as to the types of drugs it can deliver effectively and it generally does not deliver its drug charge as completely as does the presently claimed device. Moreover, the osmotic device of Wong et al. releases drug only by osmotic pumping. On the other hand, the expandable core is completely surrounded by the drug-containing layer in the presently claimed invention, and, by virtue of its construction, the claimed device delivers drug by both osmotic pumping and diffusion.

The Guittard et al. patent discloses an osmotic device very similar in construction to the device of Wong et al. The osmotic device of Guittard et al. comprises a bi-layered core surrounded by a drug-containing layer. The layers of the core are in stacked arrangement; therefore, the drug-containing layer does not completely surround the expandable layer. This type of device is limited as to the types of drugs it can deliver effectively and it generally does not deliver its drug charge as completely as does the presently claimed device. Moreover, the osmotic device of Guittard et al. releases drug only by osmotic pumping. On the other hand, the expandable core is completely surrounded by the drug-containing layer in the presently claimed invention, and, by virtue of its construction, the claimed device delivers drug by both osmotic pumping and diffusion.

The Staniforth patent discloses a drug delivery device that provides a controlled release of drug through a preformed orifice in an impermeable membrane surrounding a drug-containing core. The impermeable membrane of Staniforth does not allow passage of fluid from an environment of use into the core of the device or passage of drug from the core of the device into an environment of use. An aqueous fluid enters the core only by way of the preformed orifice and a drug containing fluids exits the core only by way of the preformed orifice. Moreover, the Staniforth device is only suitable for delivering very water soluble drugs. On the contrary, the presently claimed device includes a membrane that is permeable and that comprises a preformed orifice such that an aqueous fluid enters the core through the membrane and the preformed orifice and drug is delivered through the membrane and the preformed orifice. By virtue of its construction, the claimed device can be used to deliver drugs that range in solubility from very soluble to practically insoluble or insoluble.

Finally, none of the cited references disclose that a membrane having a preformed passageway and comprising a mixture of a cellulose acylate, a poly(methacrylate) copolymer salt and a plasticizer will be able to deliver a drug by the combined mechanisms of diffusion and osmotic pumping.

The undersigned hereby requests that this Amendment and Statement be fully considered and entered into the above-captioned International Application.

FIG. 1a

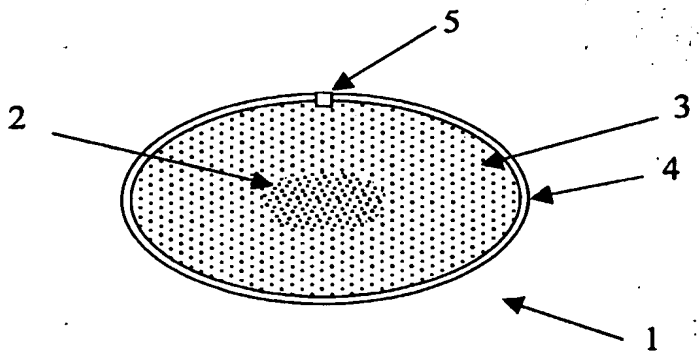
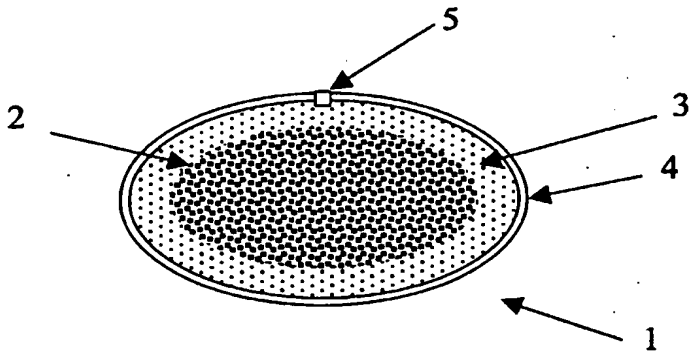


FIG. 1b



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/00562

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/20, 9/22, 9/24, 9/28, 9/30, 9/36
US CL : 424/464, 468, 471, 472, 473, 474, 475, 479, 480

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/464, 468, 471, 472, 473, 474, 475, 479, 480

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,693,886 A (AYER) 15 September 1987 (15.09.1987), see Example 3.	1, 2, 7, 8, 10, 14, 15, 17-21, 23, 32 and 34-36 --- 1, 2, 7, 8, 10, 14, 15, 17-21, 23, 32, and 34-36
X --- Y	US 4,765,989 A (WONG et al.) 23 August 1988 (23.08.1988), see examples 1-4.	1, 2, 7-11, 14, 15, 17-23, 29, 30, 32-36 and 38 --- 1-11, 14, 15 and 17-39
X --- Y	US 4,859,470 A (GUITTARD et al.) 22 August 1989 (22.08.1989), see examples 1-4.	1, 2, 7, 8, 12-14, 16-21, 23 and 32-36 --- 1, 2, 7, 8, 12-14, 16-21, 23 and 32-36

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2001 (29.03.2001)	20 APR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer P.E. McQueeney Telephone No. 703-308-1234

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/00562

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,004,614 A (STANIFORTH) 02 April 1991 (02.04.1991), see claim 2; col. 5, lines 43-57; col. 6, line 23 through col. 8, line 48.	1-11, 14, 15 and 17-39